Trihalomethanes in Drinking Water and Spontaneous Abortion

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Trihalomethanes (chloroform, bromoform, bromodichloromethane, and chlorodibromomethane) are common contaminants of chlorinated drinking water. Although animal data indicate that these compounds may be reproductive toxicants, little information exists on their relation to spontaneous abortion in humans. We examined exposure to trihalomethanes and spontaneous abortion in a prospective study of 5,144 pregnant women in a prepaid health plan. Seventy-eight drinking water utilities provided concurrent trihalomethane sampling data. We calculated total trihalomethane levels by averaging all measurements taken by the subject's utility during her first trimester. We calculated exposures to individual trihalomethanes in an analogous manner. Women who drank ≥5 glasses per day of cold tapwater containing ≥75 µg per liter total trihalomethanes had an adjusted odds ratio (OR) of 1.8 for spontaneous abortion [95% confidence interval (CI) = 1.1-3.0]. Of the four individual trihalomethanes, only high bromodichloromethane exposure (consumption of ≥5 glasses per day of cold tapwater containing ≥18 µg per liter bromodichloromethane) was associated with spontaneous abortion both alone (adjusted OR = 2.0; 95% CI = 1.2-3.5) and after adjustment for the other trihalomethanes (adjusted OR = 3.0; 95% CI = 1.4-6.6).

Key words: spontaneous abortion, trihalomethanes, drinking water, chloroform, bromoform, bromodichloromethane, chlorodibromomethane, chlorination disinfection byproducts.

Trihalomethanes (chloroform, bromoform, bromodichloromethane, and chlorodibromomethane) are common contaminants of chlorinated drinking water, formed when chlorine reacts with humic and fulvic acids in raw water.[1-3] A U.S. Environmental Protection Agency survey demonstrated that trihalomethanes are present in virtually all chlorinated water supplies.[4] Although there are many data gaps in the reproductive toxicology of these compounds,[5,6] animal studies have found possible relations between oral exposure to various trihalomethanes and fetotoxicity,[7,8] increased embryo resorption rates,[9] and sperm abnormalities.[6,10]

Few studies have examined trihalomethanes in drinking water and adverse pregnancy outcome in humans.[11] Two studies found evidence of increased risk of intrauterine growth retardation,[12,13] although one of those reports,[12] along with a third study,[14] found no meaningful association with low birthweight (<2,500 gm). Relations with neural tube and other birth defects were noted in a cross-sectional study and a case-control sample of the same population.[13,15] The only study to examine spontaneous abortion (SAB) found a modest but not dose-related association with total trihalomethanes that disappeared when water intake was also taken into account.[14] These studies were all cross-sectional or retrospective and had varying degrees of precision in exposure assessment.[11]

We recently completed a large prospective study (the Pregnancy Outcome Study, or POS), which found an association between tapwater consumption and SAB in one of three California regions examined, although the overall SAB rate did not differ much among regions.[16] Reasoning that region may be a proxy for exposure to one or more specific water constituents associated with SAB, we obtained water quality data from utilities that serviced the POS cohort. The current study examines the relation between trihalomethanes indrinking water, water consumption, and SAB.

Methods

Subjects

POS subjects were recruited from members of three facilities of a large managed health care organization (Kaiser Permanente Medical Care Program) from 1989 to 1991. The three facilities were located in areas, identified here as Regions I, II, and III, that received primarily mixed, surface, and groundwater, respectively. Recruitment occurred when women called to make theirfirst prenatal care appointment, after having had a positive pregnancy test. Eligibility criteria included being ≥18 years old, at ≤13 weeks gestation, English or Spanish speaking, and having a known date of the last menstrual period (LMP). Of 7,881 women evaluated by the prenatal clerks, 6,179 were initially eligible and willing to participate; 5,342 subjects completed acomputer-assisted telephone interview that obtained information on demographics, previous pregnancy history, employmentstatus, consumption of tap and bottled water, alcohol, tobacco, and caffeine, and other factors.

We ascertained pregnancy outcomes for 99% of the 5,342 interviewed women. Ninety-one per cent of outcomes were determined from Kaiser Permanente hospital discharge or medical records, and 8% from follow-up interviews or by matchingto the California Birth Registry. We defined an SAB as a pregnancy loss at ≤20 completed weeks of gestation, confirmed bymedical records or by interview with the study physician (KW). We treated multiple gestations (N = 55) as a single pregnancy,since they could not be identified in an unbiased manner (most SABs occurred before a ultrasound was performed). We excluded ectopic and molar pregnancies (N = 17) and pregnancies that were electively terminated (N = 128), leaving 5,144pregnancies available for analysis. Additional details regarding recruitment, interview content, and determination of pregnancyoutcome are described in the report by Swan *et al.*[16]

Exposure Assessment

Quantification of exposure to trihalomethanes was accomplished through a series of steps. (1) We used the subject's addressto determine her residential drinking water utility. Where it was not possible to assign a utility on the basis of a city or zip code, we consulted utility distribution maps and/or billing records. We identified a total of 85 drinking water utilities that served ourstudy subjects; we were able to assign 97% of the POS cohort to a utility. (2) State regulations require water utilities that use chlorination to measure levels of total trihalomethanes (TTHM, a composite measure which sums the four individualtrihalomethanes) at distribution system taps on a quarterly basis. We obtained TTHM distribution system measurements, anyindividual trhalomethane measurements, and annual water quality reports directly from the utilities. We received data from 78of the 85 utilities; these 78 utilities served 96% of the POS cohort. (3) For 77% of the cohort, we estimated TTHM level by averaging all distrbution TTHM measurements taken by the subject's utility within the subject's first trimester, defined as the LMP + 93 days (we recoded measurements below the minimum detection limit, typically 0.5 μg per liter, to zero). If measurements within a subject's frst trimester were not available, we averaged measurements taken within 30 days of thesubject's first trimester (this procedure produced TTHM levels for an additional 4% of the cohort). For 9% of the cohort who had no other data available, we used the annual average from the utility's annual water quality report. (4) We used analogous methods to estimate first trimester drinking water levels of individual trihalomethanes. Although regular testing for individualtrihalomethanes is not mandatory, we were able to obtain these measurements from most large utilities that used surface water. (5) Using information from the telephone interview, we estimated each subject's daily cold tapwater intake at 8 weeks gestation. For those women who were interviewed earlier, we used the tapwater intake in the week before interview.[16] We also calculated total tapwater intake (cold plus hot). In 53 samples of bottled water obtained randomly from POS subjects, TTHM was undetectable in 72% (minimum detection limit = 0.5 µg per liter), with a mean of 10 µg per liter in the remainder. Thus, we assumed that bottled water consumption would not contribute substantially to TTHM exposure, and we did not consider bottled water further in this analysis.

Statistical Analysis

The subjects' TTHM and individual trihalomethane levels did not follow any simple parametric distribution. For this reason, and to reduce the impact of potential misclassification, we analyzed these variables as categorical variables. We determined cutoffs for TTHM and cold tap consumption variables empirically by examining SAB rates in incremental exposure groups. We included in the low TTHM category (<75 µg per liter) women for whom first trimester TTHM levels were missing but who received water from utilities that distributed almost exclusively (≥95%) groundwater (N = 274; no subject with known TTHM levels receiving ≥95% groundwater had levels >19 µg per liter).

We then created a dichotomous variable that combined the first trimester TTHM exposure variable and cold tapwater consumption. We defined high "personal TTHM exposure" as drinking ≥5 glasses of cold tapwater per day *and* having a TTHM level ≥75 µg per liter. We defined low personal exposure as either drinking <5 glasses of cold tapwater per day, having a TTHM level <75 µg per liter, *or* receiving water from a utility that provided ≥95% groundwater. The proportion of subjects with unknown personal TTHM exposure was low (0.7%) and did not differ much by region or by SAB status.

We defined personal exposures to chloroform, bromoform, bromodichloromethane, and chlorodibromomethane in an analogous manner. We defined high personal exposure as drinking ≥5 glasses per day of cold tapwater *and* having a first trimester trihalomethane level in the upper quartile (≥17 µg per liter for chloroform, ≥16 µg per liter for bromoform, ≥18 µg per liter for bromodichloromethane, and ≥31 µg per liter for chlorodibromomethane). We defined low personal exposure as either drinking <5 glasses per day of cold tapwater, having a trihalomethane level below the cutoff, or (if the trihalomethane level was missing) having a TTHM level less than the cutoff minus 3 µg per liter.

We first examined the relations between exposure variables and SAB using contingency tables. We also examined several demographic, socioeconomic, life-style, and reproductive history variables using contingency tables and multiple logistic regression models. Variables that proved to be independent risk factors for SAB in our data included gestational age at interview (≤8 *vs* >8 weeks), maternal age at interview (≥35 *vs* <35 years), cigarette smoking (any *vs* none), history of pregnancy loss (≥2 *vs* <2 prior SABs), maternal race (black and Asian *vs* white, Hispanic), and employment during pregnancy. We constructed multiple logistic regression models for all water-related exposures using these covariates, so that we could compare the results. Although lack of nausea during pregnancy was strongly associated with SAB in our data, it may be on the causal pathway to SAB, and controlling for it may be inappropriate.[17] None of the odds ratios (ORs) produced by our models that included nausea differed from ORs produced by models excluding nausea by more than 10%; we report here only the adjusted ORs from models that do not include nausea.

Results

Characteristics of Cohort

Several demographic characteristics of the study cohort are described in Table 1. Average age of the subjects was 27.9 years [range = 18-47 years; standard deviation (SD) = 5.1], and the overall SAB rate was 9.7%. Distributions of various water exposure variables are shown in Tables 2 and 3. The mean first trimester TTHM level was 46.5 µg per liter (N = 4,622; range = 0-157 µg per liter; SD = 32.8).

TABLE 1

Demographic and Life-Style Characteristics of 5,144 Women Participating in the Pregnancy Outcome Study

Variable	Number	%*
Maternal age (years)		
<35	4,583	89.1
≥ 35	561	10.9
Gestational age at interview (weeks)		
≤ 8	3,287	63.9
>8	1,847	35.9
Pregnancy history		
Nulliparous	1,320	25.7
Multiparous, <2 prior SABs	3,569	69.4
Multiparous, ≥ 2 prior SABs	247	4.8
Race		
White	3,390	65.9
Hispanic	945	18.4
Asian	416	8.1
Black	330	6.4
Other	59	1.1
Employment during pregnancy		
Employed	4,064	79.0
Not employed	1,080	21.0
Highest educational level of subject or spouse		
High school or less	1,624	31.6
At least some college	3,517	68.4
Highest weekly alcohol consumption during pregnancy		
None	2,723	52.9
Sips	2,087	40.6
≥ 1 drink/week	334	6.5
Cigarette consumption in week before interview		
None	4,607	89.6
Any	536	10.4
Location of residence		
Region I	1,646	32.0
Region II	1,757	34.2

Region III	1,741	33.8

* Percentages may not sum to 100 because of missing values.

TABLE 2

Characteristics of Tapwater Exposure among 5,144 Women Participating in the Pregnancy Outcome Study

Variable	Number	%*
Consumption of cold tapwater at 8 weeks' gestation (glasses/day)		
0	1,925	37.4
0.5-4	2,449	47.6
≥5	767	14.9
Consumption of tapwater (hot + cold) at 8 weeks' gestation (glasses/day)		
0	1,463	28.4
0.5-4	2,554	49.7
≥5	1,124	21.9
Filter use†		
None	2,574	80.0
Activated carbon	203	6.3
Reverse osmosis	133	4.1
Filter type unknown/other	296	9.2
Usual method of drinking tapwater†		
Straight from tap	1,850	57.5
Refrigerate and/or let stand	1,357	42.2
Showering (minutes/week)		
0-105	3,692	71.8
>105	922	17.9

* Percentages may not sum to 100 because of missing values.

† Percentages are of women drinking any cold tapwater.

TABLE 3

Percentage of Pregnancies Ending in Spontaneous Abortion (SAB), by Source of Tapwater and First Trimester Trihalomethane Levels, among 5,144 Women Participating in the Pregnancy Outcome Study

Variable	Number (% of Total*)	% SAB*	*P*-Value†
Source of tapwater			
Ground	414 (8.0)	8.5	
Mixed	3,191 (62.0)	9.2	
Surface	1,403 (27.3)	10.8	0.17
TTHM (μg/liter)			
0 (nondetectable)	332 (6.5)	7.8	

1-14	754 (14.7)	8.8	
15-29	322 (6.3)	7.8	
30-44	922 (17.9)	10.8	
45-59	550 (10.7)	7.3	
60-74	792 (15.4)	9.8	
75-89	278 (5.4)	10.8	
90-104	458 (8.9)	10.9	
105-119	169 (3.3)	12.4	
≥120	45 (0.9)	15.6	0.16
Unknown, ground‡	274 (5.3)	9.9	
Unknown, surface/mixed‡	248 (4.8)	11.3	
Chloroform (μg/liter)			
0-3	701 (13.6)	8.1	
4-16	1,548 (30.1)	10.7	
≥17	903 (17.6)	9.5	0.15
Bromoform (μg/liter)			
0	865 (16.8)	9.2	
1-15	1,345 (26.1)	9.8	
≥16	942 (18.3)	10.3	0.76
Bromodichloromethane (μg/liter)			
0-2	691 (13.4)	9.1	
3-17	1,635 (31.8)	9.8	
≥18	826 (16.1)	10.3	0.74
Chlorodibromomethane (μg/liter)			
0	536 (10.4)	9.7	
1-30	1,805 (35.1)	9.6	
≥31	811 (15.8)	10.4	0.83

* Percentages may not sum to 100 because of missing values.

† *P*-value based on chi^2.

‡ Unable to estimate first trimester TTHM level, but utility known to obtain water from ground or surface/mixed sources.

TTHM and Spontaneous Abortion

When we examined SAB rates by first trimester TTHM levels in 15-μg per liter increments, we noted that SAB rates remained fairly stable until 75 μg per liter, when they began to rise (Table 3). When we dichotomized TTHM level at 75 μg per liter, however, the increase in risk associated with higher exposure appeared modest (Table 4). When we split the cohort by amount of cold tapwater consumption, women consuming <5 glasses per day of cold tapwater showed little increase in risk with high TTHM levels. In contrast, the adjusted OR associated with a high TTHM level among women drinking≥5 glasses per day of cold tapwater was 2.0 [95% confidence interval (CI) = 1.1-3.6]. When we combined TTHM level and coldtapwater consumption into a personal exposure variable (see Methods), women with high personal TTHM exposure had anadjusted OR of 1.8 (95% CI = 1.1-3.0). SABs in women with high personal TTHM exposure occurred on average 1 week earlier than SABs in other women (10.2 *vs* 11.2 weeks of gestation).

TABLE 4

Percentage of Pregnancies Ending in Spontaneous Abortion (SAB) and Odds ratios (ORs) for SAB, among 5,144 Women Exposed to Varying Levels of Total Trihalomethanes (TTHMs) in Their Residential Drinking Water during Their First Trimester of Pregnancy

TTHM (µg/liter)	Cold Tapwater (Glasses/Day)	% SAB	N	OR† (95% CI)	OR‡ (95% CI)
<75§	N/A‖	9.1	3,672	1.0	1.0
≥75	N/A	11.4	950	1.3 (1.0-1.6)	1.2 (1.0-1.5)
<75§	<5	9.2	3,105	1.0	1.0
≥75	<5	10.8	828	1.2 (0.9-1.5)	1.1 (0.9-1.4)
<75§	≥5	8.5	565	1.0	1.0
≥75	≥5	15.7	121	2.0 (1.1-3.6)	2.0 (1.1-3.6)
Low personal TTHM exposure*,§		9.5	4,988	1.0	1.0
High personal TTHM exposure*		15.7	121	1.8 (1.1-2.9)	1.8 (1.1-3.0)

* See text for definition of personal TTHM exposure.

† Unadjusted OR.

‡ Adjusted by logistic regression for gestational age at interview (≤8 *vs* >8 weeks), maternal age at interview (≥35 *vs* <35 years), cigarette smoking (any *vs* none), history of pregnancy loss (≥2 *vs* <2 prior SABs), maternal race (black and Asian *vs* white, Hispanic), and employment during pregnancy.

§ Referent category.

‖N/A = not applicable.

Sources of TTHM exposure via routes other than ingestion include showering and swimming. Although bivariate analysis ofshowering and SAB showed a slight dose-related increase in risk among women with TTHM levels≥75 µg per liter, showering >105 minutes per week (an average of >15 minutes per day) was not an independent risk factor for SAB whenincluded in a model with personal TTHM exposure and other covariates (OR = 1.0; 95% CI = 0.8-1.3). Two hundred twenty-two (4.3%) subjects reported swimming≥2 times per week. The overall SAB rate in this group was low (7.7%). Excluding swimmers from the cohort did not change the OR for personal TTHM exposure.

Factors That Alter Trihalomethane Levels

We examined two factors that can decrease the concentration of trihalomethanes in tapwater, the use of home water filters and letting tapwater stand before drinking it, among women with high personal TTHM exposure. A slightly smaller proportion offilter users had an SAB (14.3% of 28) than did women who drank unfiltered water (16.1% of 93). Women who drank water straight from the tap had a higher SAB rate than women who let tapwater sit before drinking it (17.6% of 74 *vs* 13.0% of 46). In women with low personal TTHM exposure, neither filter use nor method of water consumption made a difference in SABrate (all regions combined).

Heating can volatilize and thus reduce TTHM levels in tapwater. To examine the effect of heating, we recalculated personal TTHM exposure using total tapwater consumption (hot plus cold). This recalculation resulted in an adjusted OR of 1.2 for highpersonal exposure (N = 5,076; 95% CI = 0.8-1.9), which was substantially lower than the OR of 1.8 for high personalTTHM exposure calculated using cold tapwater alone.

Since our interview ascertained tapwater consumption at home, a potential source of misclassification of TTHM exposure was water consumption outside the home. Reasoning that the exposure assessment for women who did not work outside the home might be more accurate than that for employed women, we compared results for these two groups. Table 5 shows that the OR for high personal TTHM exposure among women not working outside the home was twice that of women employed at some time during pregnancy. Although the high OR among nonemployed women was enhanced by a low SAB rate among womenwith low TTHM exposure (7.8%), the SAB rate in the high exposure/nonemployed group was still high (20%).

TABLE 5

Relation between Personal Exposure to Total Trihalomethanes (TTHM)* and Odds of Spontaneous Abortion (SAB) by Employment Status Outside the Home during Pregnancy, and by Region

Subgroup and Personal TTHM Exposure	% SAB	N	OR† (95% CI)	OR‡ (95% CI)
Not employed				
Low§	7.8	1,039	1.0	1.0
High	20.0	30	3.0 (1.2-7.4)	3.0 (1.2-7.9)
Employed				
Low§	9.9	3,949	1.0	1.0
High	14.3	91	1.5 (0.8-2.7)	1.5 (0.8-2.8)
Region I				
Low§	8.9	1,614	1.0	1.0
High	24.1	29	3.2 (1.4-7.7)	4.3 (1.8-10.6)
Region II				
Low§	9.7	1,656	1.0	1.0
High	14.0	86	1.5 (0.8-2.8)	1.5 (0.8-2.9)
Region III				
Low§	9.8	1,718		
High	0.0	6	N/A‖	N/A

* See text for definition of personal TTHM exposure.

† Unadjusted OR.

‡ Adjusted by logistic regression for gestational age at interview (≤8 *vs* >8 weeks), maternal age at interview (≥35 *vs* <35 years), cigarette smoking (any *vs* none), history of pregnancy loss (≥2 *vs* <2 prior SABs), and maternal race (black and Asian *vs* white, Hispanic). The analysis by region was also adjusted for employment during pregnancy.

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§ Referent category.

||N/A = not applicable.

Individual Trihalomethanes

Region was not an independent risk factor for SAB when examined with personal TTHM exposure and other covariates in a logistic regression model. When examined separately, however, the personal TTHM effect was much more pronounced in Region I than in Region II (Table 5). (Region III, with its preponderance of groundwater utilities, had too few women in the high exposure group for comparison.) The mean TTHM level among Region I women in the high personal exposure group was 93 µg per liter (N = 29; SD = 10.4; range = 78-105 µg per liter), which differed little from the mean TTHM level in Region II (92 µg per liter, N = 86; SD = 9.3; range = 75-123 µg per liter). The amount of cold tapwater consumed by women with high personal TTHM exposure also did not differ much between the three regions, with mean daily consumption of 7.3 and 6.9 glasses per day (Regions I and II, respectively). Region I women, however, consumed water containing proportionately more bromodichloromethane and chlorodibromomethane.

Analysis of personal exposure to chloroform, bromoform, bromodichloromethane, and chlorodibromomethane demonstrated that bromodichloromethane had the strongest association with SAB (adjusted OR = 2.0; 95% CI = 1.2-3.5) (Table 6). When we included all four individual trihalomethane variables, along with the covariates, simultaneously in a logistic regression model, high personal bromodichloromethane exposure had an OR of 3.0 for SAB (95% CI = 1.4-6.6).

TABLE 6

Odds Ratios for Spontaneous Abortion Associated with High Personal Exposure to Chloroform, Bromoform, Bromodichloromethane, or Chlorodibromomethane,* among 5,144 Women in the Pregnancy Outcome Study

	OR (95% CI)†			
Trihalomethane	All Regions	Region I	Region II/III	All Regions‡
Chloroform	0.9 (0.5-1.6)	1.4 (0.5-4.1)	0.8 (0.4-1.5)	0.6 (0.3-1.2)
Bromoform	1.0 (0.5-2.0)	1.3 (0.4-4.5)	1.0 (0.5-2.1)	0.7 (0.2-2.1)
Bromodichloromethane	2.0 (1.2-3.5)	2.1 (0.9-4.5)	2.3 (1.1-4.9)	3.0 (1.4-6.6)
Chlorodibromomethane	1.3 (0.7-2.4)	1.3 (0.4-3.7)	1.4 (0.6-3.2)	0.8 (0.2-2.8)

* See text for definition of high personal exposure to the individual trihalomethanes.

† In the first three columns, each OR represents results from a separate logistic regression, adjusted for gestational age at interview (≤8 *vs* >8 weeks), maternal age at interview (≥35 *vs* <35 years), cigarette smoking (any *vs* none), history of pregnancy loss (≥2 *vs* <2 prior SABs), maternal race (black and Asian *vs* white, Hispanic), and employment during pregnancy. Other trihalomethanes were not included as covariates in these analyses.

‡ The last column presents results from a single logistic regression, adjusted for the above covariates and all four individual trihalomethanes simultaneously.

Discussion

We found a modest association between ingestion of tapwater containing trihalomethanes and SAB, with risk beginning to increase around 75 µg per liter TTHM. As expected, risk was modified by the amount of cold tapwater consumed, with an adjusted OR of 1.8 (95% CI = 1.1-3.0) for women who, during their first trimester, drank $\geq$5 glasses per day of cold tapwater containing an average TTHM level of $\geq$75 µg per liter. Two activities that could contribute to TTHM exposure via routes other than ingestion (showering and swimming) appeared to exert little additional effect. Small numbers impaired the assessment of effect modification by filtering and letting drinking water stand, although differences in SAB rates were in the direction one would expect given a volatile agent. Finally, results were stronger in women not employed outside the home, for whom our home-based exposure assessment should be more precise

The primary limitation of our study was potential misclassification of exposure. Although trihalomethane levels can change rapidly over short periods of time, levels for most subjects were based on a single day's testing. Averaging TTHM levels from several sampling sites within a utility's boundaries introduced another source of misclassification. Degree of misclassification however, was not likely to differ between SABs and non-SABs, meaning that bias would be toward the null. Another limitation was that we could not fully characterize exposure to trihalomethanes via routes other than ingestion; for example, we did not ascertain activities such as washing dishes and clothes and bathing. These activities, however, would tend merely to augment exposure in already exposed individuals, since the same water would usually be used for drinking.

Despite the potential for exposure misclassification, our study had many strengths. The prospective design avoided problems with recall and selection bias (particularly important for the water consumption variables), and our follow-up of pregnancy outcome was virtually complete. The geographic diversity of our cohort and the large number of utilities involved resulted in a wide range of trihalomethane exposures. We derived TTHM levels for most subjects from measurements taken during the first trimester of pregnancy. We were also able to obtain individual trihalomethane measurements for a majority of study subjects. Thus, this study addresses most of the research recommendations put forth by a panel convened by the U.S. Environmental Protection Agency and the International Life Sciences Institute.[11]

Only one other study has examined the relation between trihalomethane exposure and SAB. In a case-control study of medically treated SAB, preterm delivery, and low birthweight in North Carolina, Savitz *et al*[14] found an adjusted OR of 1.2 for SAB in the highest tertile of TTHM concentration (95% CI = 0.6-2.4; TTHM range = 81-169 µg per liter). This result is consistent with our finding of an adjusted OR of 1.2 when we dichotomized the TTHM level at 75 µg per liter. Savitz *et al* saw a stronger association in the highest TTHM sextile (adjusted OR = 2.8; 95% CI = 1.2-6.1; TTHM range not specified), but there was no dose-related trend. Savitz *et al* also found no association between TTHM dose (concentration × glasses per day) and SAB. This result may have reflected their finding that, in general, water intake was inversely related to risk. Our method of combining dichotomous TTHM and water intake variables, rather than calculating a TTHM dose, had the advantage of reducing this potential bias.

In our study, both the composition of TTHM and the risk of SAB associated with high personal TTHM exposure varied by region. The ORs for individual trihalomethanes were similar across regions, however. Bromodichloromethane (or some compound highly correlated with it) was the trihalomethane most strongly associated with SAB. Although there is little previous research regarding the reproductive effects of this compound, one study recently reported that oral administration of bromodichloromethane was related to full-litter resorptions in pregnant rats.[9]

Swan *et al*[16] found a dose-related increase in SABs among tapwater drinkers in Region I, but not in Regions II or III. Exposure to TTHM or bromodichloromethane does not entirely explain this association, since a tapwater effect is still evident among Region I women with low levels of both TTHM and bromodichloromethane. Furthermore, the initial studies in Region I found the strongest effect in areas served only by unchlorinated groundwater.[18,19] Thus, it is likely that other factors contributed to the tapwater effect described by Swan *et al.*

It is not unusual for the concentration of TTHM to exceed 75 µg per liter in chlorinated drinking water, the threshold identified with increased risk of spontaneous abortion in women who drank 5 or more glasses daily. 18.4% of our cohort was exposed to water with TTHM at levels of ≥75 µg per liter during the first trimester, with levels ranging up to 157 µg per liter. The Maximum Contaminant Level (MCL) permissible for TTHM in drinking water by state and federal law at present is an average of 100 µg per liter sampled over four consecutive quarters.[20] Individual trihalomethanes and other chlorinated disinfection byproducts are not regulated by federal law. More accurate means of exposure assessment, including home tapwater sampling or more sophisticated modeling techniques, may help clarify the effect of these water contaminants on reproduction.

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